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Long-term, multi-center evaluation of subconjunctival injection of triamcinolone for non-necrotizing, non-infectious anterior scleritis

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Abstract

Purpose—We sought to characterize the long-term outcomes and complications of subconjunctival triamcinolone acetonide injection (STI) for non-necrotizing, non-infectious anterior scleritis.

Design—Retrospective, interventional, noncomparative, multi-center study.

Participants—Sixty-eight eyes of 53 patients from nine participating hospitals in the United States, Singapore, and Australia. Only eyes with 6 or more months of follow-up were included.

Intervention—Subconjunctival injection of 2 to 40 mg of triamcinolone acetonide was administered to eyes with non-necrotizing, non-infectious anterior scleritis.

Main Outcome Measures—Resolution of signs and symptoms; time to recurrence of scleritis; side effect profile.

Results—Median follow-up was 2.3 years (range 6 months to 8.3 years). Sixty-six eyes (97.0%) experienced improvement of signs and symptoms after one injection. Twenty-four months after a single injection, 67.6% of eyes remained recurrence-free, while at 48 months, 50.2% were recurrence-free. 55.0% of patients who had adverse effects from systemic medications were off all systemic medications at last follow-up; 55.0% of patients who were on systemic medications at the time of first triamcinolone acetonide injection were off prednisone and immunosuppressants at this time; 76.2% of patients still needing systemic agents had associated systemic disease. Fourteen eyes (20.6%) had ocular hypertension not requiring intraocular pressure (IOP)-lowering therapy. Two eyes (2.9%) were treated with topical IOP-lowering agents alone while two needed surgical intervention for glaucoma. None developed scleral necrosis or melt.

Conclusions—This retrospective, international study carried out at nine hospitals suggests that STI can treat non-necrotizing, non-infectious anterior scleritis with side effects limited to elevated IOP in a few patients. Though no cases of scleral melt or necrosis were observed, we cannot definitively conclude that this may not occur after STI. Intraocular pressure should be closely monitored after STI. STI may be useful as adjuvant therapy or to decrease systemic medication burden.

Non-necrotizing, non-infectious scleritis is the most common form of anterior scleritis; this potentially sight-threatening condition is characterized by inflammation of the sclera leading to deep pain and redness.¹ Typically associated with systemic rheumatic disease,² treatment for anterior scleritis often requires oral medication such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Immunosuppressive drugs may also be used in recurrent and refractory cases, as well as in those needing corticosteroid-sparing therapy.³ However these drugs carry significant risk of morbidity because of their adverse or toxic systemic effects. Thus, local therapy to avoid adverse systemic effects for treatment of this condition is desired.

While classic teaching purports that subconjunctival application of steroids for scleritis is controversial, if not dangerous, due to the alleged risk of scleral necrosis and melt,^{4–6} there have been several published series of patients who have received periocular triamcinolone acetonide injection for non-necrotizing, non-infectious anterior scleritis.^{7–12} Our initial experiences^{7,10} using this intervention revealed no cases of scleral thinning or necrosis, but long-term follow-up of these small series was lacking. We sought to expand our study to multiple independent clinical centers around the world with longer follow-up to evaluate

outcomes, time to recurrence, and side-effect profile of subconjunctival triamcinolone acetonide injection (STI) for this form of scleritis.

Methods

This retrospective, interventional, noncomparative study conducted in the United States, Australia, and Singapore followed the guidelines of the Declaration of Helsinki and was approved by the local ethics committee from each clinical center. The coordinating center was Doheny Eye Institute / University of Southern California + Los Angeles County (USC + LAC) Hospital. All patients who were treated with STI for non-necrotizing, non-infectious anterior scleritis (diffuse or nodular) at one of the following nine hospitals were included: Doheny Eye Institute (Los Angeles, CA), USC + LAC Hospital (Los Angeles), University of Alabama at Birmingham (Birmingham, AL), Associated Vitreoretinal and Uveitis Consultants (Indianapolis, IN), Texas Retina Associates (Dallas, TX), Liverpool Hospital (New South Wales, Australia), St. Vincents Hospital (Sydney, Australia), Bascom Palmer Eye Institute (Miami, FL), and Singapore National Eye Centre (Singapore).

All patients underwent detailed ophthalmic and systemic evaluation including visual acuity, intraocular pressure (IOP) measurement, slit-lamp biomicroscopic examination, dilated fundus examination, and medical, laboratory, and radiologic evaluation for associated systemic diseases. Patients included in this series had diffuse or nodular anterior scleritis who were already on topical drops (prednisolone, NSAIDs) for scleritis and/or systemic medication (prednisone, NSAIDs, methotrexate, cyclophosphamide, indomethacin, azathioprine, etanercept, infliximab, cyclosporine, mycophenolate mofetil) for scleritis and associated systemic condition. Patients who had follow-up of less than six months after STI, ocular hypertension (defined as IOP > 21 mm Hg), history of glaucoma or steroid response, necrotizing features (defined as scleral thinning or destruction of the sclera, evidence of vascular closure on red-free examination, and/or uveal show), and associated infections such as tuberculosis, syphilis, herpes zoster, cat-scratch and Lyme disease were excluded from this series. After STI, systemic medications were gradually tapered if resolution of signs and symptoms was achieved. If a patient was receiving medications for a systemic condition, the rheumatologist or internist was informed that scleritis was successfully treated locally, and their judgment would determine when and how to taper medication based on systemic activity.

In general, follow-up evaluations were performed at 1–2 weeks, 1 month, and 1- to 3-months after STI and included full ophthalmic examination, IOP measurement and time for resolution of symptoms. Special attention was given to evaluation of scleral thinning or necrosis. Resolution at 1 month prompted gradual tapering of topical drops and systemic medications. Side effects from prior treatment were also noted. If IOP was elevated greater than 21 mmHg at any visit, clinical judgment by the principal investigator at each site guided the necessity for visual field testing, medical therapy for elevated IOP and glaucoma consultation.

Time to recurrence of scleritis was calculated using the Kaplan-Meier method.¹³ Chi-square test was used to assess the possible association between the presence of underlying systemic disease and the use of systemic therapy at the most recent follow-up, as well as the frequency of re-treatments. A p value ≤ 0.05 was regarded as statistically significant.

Subconjunctival injection procedure

The technique of injection has been described previously.⁷ Briefly, eyes were anesthetized with topical 0.5% proparacaine drops and cotton-tipped applicators soaked with proparacaine. For nodular scleritis, 0.05 to 0.1 mL of triamcinolone acetonide (Kenalog 40

mg/mL) was injected with a 25- or 27-gauge needle under the conjunctiva immediately adjacent to the nodule. Those with diffuse scleritis received up to 0.2 mL per inflamed quadrant.

Results

Ninety-six eyes of 81 patients were administered STI between August 1999 and December 2009 at nine participating hospitals. Twenty-four eyes in 24 patients were excluded because follow-up was less than six months; two eyes were excluded for pre-existing necrotizing disease, and two were excluded for infectious etiology. Thus, 68 eyes of 53 patients were enrolled in the study. See Table 1 for a summary of clinical and demographic information. Fifteen (28.3%) patients were male and 38 (71.7%) were female. Median age was 46.7 (range 24–75) years. Thirty-eight (55.9%) right eyes and 30 (44.1%) left eyes were administered STI. Diffuse scleritis was treated in 39 eyes (57.4%) while nodular scleritis was seen in 32 eyes (47.1%). Three eyes had both diffuse and nodular scleritis. Median duration of scleritis prior to first STI was 6 months (average 19.5 months, range 1 week to 156 months). A total of 112 STIs were performed in these 68 eyes (median 1 injection per eye; average 1.6 injections per eye). Median follow-up was 28 months (average 33.6, range 6–100 months). Signs and symptoms improved in 66 eyes (97.0%) and completely resolved in 61 eyes (89.7%) after one STI (Fig 1). One eye had incomplete response but achieved local response after an additional STI. One eye with incomplete response was given an orbital floor injection of corticosteroid. Twenty-three eyes (33.8%) required at least a second injection at some point during follow-up; seven (10.3%) were given more than two injections. One patient with Crohn's disease, on prednisone at first STI, had 13 total injections for recurrent, diffuse anterior scleritis but exhibited no evidence of scleral thinning or necrosis despite 96 months of follow-up (Fig 2); at last follow-up this patient was no longer on systemic medication. Kaplan-Meier survival curve (Fig 3) shows that 24 months after one STI, 67.6% of eyes remained recurrence-free and 50.2% were recurrence-free 48 months after one STI. Median time to recurrence in those that did recur after a single injection was 6 months.

Systemic associations and impact of STI on oral medications

In 27 (50.9%) patients, no systemic association was found on history, examination, or laboratory evaluation (Table 2). Of those with an associated autoimmune condition, eight had rheumatoid arthritis, six had relapsing polychondritis, three had positive anti-nuclear antibodies but no evidence of systemic lupus erythematosus, two had systemic lupus erythematosus, three had Wegener's granulomatosis, one had mixed connective tissue disorder and two had Crohn's disease.

Prior to STI, 51 patients (96.2%) were taking oral NSAIDs, prednisone and/or immunosuppressants. At last follow-up visit, 23 patients (43.4%) were taking prednisone and/or immunosuppressants—at least five of these patients were being treated only for systemic disease by a rheumatologist or internist. Sixteen of 21 patients (76.2%) on prednisone and/or immunosuppressive agents at last follow-up had associated systemic disease. Frequency for systemic therapy at most recent follow-up was lower for patients with idiopathic (26.9%) versus associated systemic disease (65.4%), $p=0.005$. One pregnant patient with scleritis could not tolerate the risk of systemic medications and, thus, received STI after topical treatment failed. Three patients increased their systemic medication after one STI as they did not desire additional injection; one of these patients later had three STIs when the contralateral eye developed anterior scleritis. Though not all patients were directly questioned, 14 (26.4%) reported side effects from prior systemic therapy (e.g., osteoporosis, diabetes mellitus, weight gain, alopecia, liver toxicity, cushingoid features, insomnia,

gastritis, anxiety, headache). By last follow-up five of those 14 patients were off systemic medications.

Frequency for re-treatment was similar for patients with associated systemic disease (40.7%) compared to those with idiopathic anterior scleritis (38.5%), $p=0.87$. No statistically significant difference in re-treatment frequency was observed between patients on prednisone alone, prednisone plus immunosuppressant therapy, or no systemic medication. Moreover, pre-injection months of disease did not demonstrate a statistically significant difference in whether a patient was on or off systemic therapy at most recent follow-up.

Side effects of STI

Subconjunctival triamcinolone acetonide injection was relatively well-tolerated and desired by patients, especially those with bilateral disease who had success from the first eye. However, some experienced local side effects (Table 2). Of the 68 eyes in this study, seven (10.3%) had subconjunctival hemorrhage that resolved spontaneously. Some eyes already had cataract surgery due to long-term use of prednisone; four eyes (5.9%) in this series had cataract extraction and intraocular lens placement, while two (2.9%) had cataracts not needing surgery. All patients that had cataract or cataract extraction had a history of systemic prednisone use. Fourteen eyes (20.6%) developed ocular hypertension at some point during follow-up but fortunately did not require medical intervention. Two eyes (2.9%) needed IOP-lowering drops while two required surgical intervention (trabeculectomy; tube shunt). While initial, maximum, and final IOP were collected for each eye given STI, onset of ocular hypertension after STI was not examined. No eyes in this study developed scleral necrosis or melt (Fig 2).

Discussion

In this multi-center, long-term, retrospective study of treatment for non-necrotizing, non-infectious anterior scleritis, we found that for 68 eyes of 53 patients, nearly all experienced improvement in signs and symptoms after STI with follow-up ranging to 100 months. After one STI, two-thirds of eyes remained free of recurrence for two years. Half of patients who had adverse effects from systemic medications were off systemic medications at last follow-up. While one-fifth of eyes experienced ocular hypertension not requiring intervention, only 3% needed topical IOP-lowering agents and 3% needed surgery for glaucoma. No eyes developed scleral necrosis or melt.

Subconjunctival triamcinolone acetonide injection appears to be a useful treatment for scleritis even in persistent cases when the patient is on systemic medication. Ninety-seven percent of the eyes treated with STI experienced an improvement in signs and symptoms after a single injection; 90% had complete resolution after one STI. Some of these recalcitrant cases were given additional STIs to achieve local control. Nearly all patients were taking systemic medication at the time of STI but by last follow-up, less than half of these patients were still on systemic medication. It is plausible that some of these cases represented stability of systemic disease; but if scleritis was still active, these patients would still be on immunosuppressant therapy. Future prospective studies are required to address time to discontinuation of systemic medications after STI. Moreover 14 patients experienced toxicity (including osteoporosis, diabetes mellitus, weight gain, alopecia, liver toxicity, cushingoid features, insomnia, gastritis, anxiety, headache) from systemic medications; but after STI five of those patients were weaned off systemic therapy. As this was a retrospective, noncomparative study, it is difficult to conclude for certain whether these five patients would have been off systemic medications without STI. Nevertheless, these patients may also have had particularly recalcitrant local and/or systemic disease that made tapering of systemic medications difficult despite STI. The effect of STI is lasting, with half of

treated eyes remaining recurrence-free four years after a single injection. Thus, STI may be an acceptable therapy for patients who cannot tolerate systemic medications or for those with anterior scleritis resistant to traditional therapy.

This study represents the largest series, with longest follow-up, to date of patients receiving periocular steroid for anterior scleritis. Eleven eyes had more than six years of follow-up examinations, and 23 eyes had multiple STIs (one eye sustained 13 injections with over eight years of follow-up [figure 2]). No eyes developed scleral melting, a potentially devastating complication that has been alleged to occur very rarely.¹⁴ In contrast, we have not seen this complication in a single patient with up to 100 months of follow-up. Moreover, scleral necrosis is part of the natural history of scleritis in some patients. Thus, to establish causality between STI and later scleral necrosis would require a study demonstrating higher incidence of this alleged risk after STI than the natural history or compared to the risk in patients receiving systemic treatment for anterior scleritis. To our knowledge, no such study has been conducted; therefore, no causality has been shown between STI and scleral necrosis.

The rate of ocular hypertension not needing intervention was 20% (95% confidence interval: 10.5–29.5%) in this study. Though substantial, the number of patients needing IOP-lowering medication or glaucoma surgery was much lower. The incidence of ocular hypertension from STI is lower than that from intravitreal triamcinolone, where the post-injection ocular hypertension incidence in one long-term study was as high as 80%; 56% of those eyes required glaucoma therapy, and 9% eyes needed trabeculectomy.¹⁵ Although the STI was administered anteriorly, the low dose of triamcinolone acetonide and the subconjunctival location of the steroid (allowing faster egress from the ocular surface) may account for the lower incidence of IOP elevation. While we did not examine the time of onset of ocular hypertension after injection, this could be addressed in a future study.

Six eyes in this study developed cataracts; four of these were visually significant, requiring cataract extraction and intraocular lens placement. All six patients were receiving oral prednisone at the time of STI, and some were still on prednisone at final follow-up. Though STI could have caused or exacerbated cataract formation, timing of cataract surgery was not directly evaluated in relation to STI; it is possible that cataracts were also due to systemic prednisone therapy.

Limitations of this study include the noncomparative use of therapy in a retrospective setting. Patient selection was limited to those with non-necrotizing, non-infectious scleritis with no history of steroid response, ocular hypertension, or glaucoma. We cannot reliably extrapolate or speculate on the use of STI in other forms of scleritis.

This study adds to the mounting evidence that STI can treat anterior scleritis with a manageable side effect profile. It allowed decreased dependence on systemic medications that have considerable risk of complications. In the absence of a randomized controlled trial, we felt that studying this intervention at a high number of clinical centers with multiple independent investigators in different continents was the best method to evaluate outcomes and safety of STI. Until a randomized, controlled trial can be done definitively comparing STI to traditional therapy, STI with close monitoring of IOP may be considered in patients with non-necrotizing, non-infectious anterior scleritis who do not have a history of elevated IOP.

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Figure 1.

A, Diffuse anterior scleritis prior to subconjunctival triamcinolone injection (STI). B, Same eye as A with resolved scleritis after STI. C, Nodular scleritis prior to STI. D, Same eye as C with resolved scleritis after STI.

Figure 2.

A, Temporal sclera of patient with diffuse anterior scleritis after 13 subconjunctival triamcinolone injections over 96 month follow-up demonstrating lack of scleral thinning or necrosis. B, Nasal sclera of same patient as in A.

Figure 3.

Kaplan-Meier survival curve of time to recurrence of scleritis after initial subconjunctival triamcinolone injection. 12 months after subconjunctival triamcinolone injection, 70% were recurrence-free; at 2 years, 67.6% were recurrence-free; at 4 years, 50.2% were recurrence-free.

Table 1

Clinical and demographic information about patients treated with subconjunctival triamcinolone injection

Eyes	Patients	M	F	OD	OS	Autoimmune disorder	Systemic tx before STI	Systemic tx at last f/u	Improved post-STI	Retreated
68	53	15	38	38	30	26	51	23	66	23

STI = subconjunctival triamcinolone acetonide injection; M = male; F = female; tx = treatment; OD = right eye; OS = left eye f/u = follow-up; sxs = symptoms; w/ = with

Table 2

Side effects from scleritis treatment

	From prior systemic therapy [*]	From STI				
		OHTN w/o meds	Glaucoma w/ gtt's only	Glaucoma needing surg	Cataract	CE/IOL SCH
#	14	14	2	2	2	4
%	26.4	20.6	2.9	2.9	2.9	5.9
						10.3

STI = subconjunctival triamcinolone acetate injection; OHTN = ocular hypertension; w/o = without; w/ = with; gtt's = drops; surg = su CE/IOL= cataract extraction with intraocular lens; SCH = subconjunctival hemorrhage

* Side effects include: osteoporosis, diabetes mellitus, weight gain, alopecia, liver toxicity, cushingoid features, insomnia, gastritis, anx